REMARKS

The Office Action of January 4, 2006 presents the examination of claims 3-7,, 9-11 and 13, claims 1, 2, 8, 12, 14-45 being withdrawn from consideration pursuant to a restriction requirement.

The specification is amended to delete browser executable hyperlinks as required by the Examiner, and generic description of the named databases is provided instead.

The present paper cancels claims 1, 2, 8, 12 and 17-45. New claims 46-48 are added. Claims 3-5 are amended to restrict their scope to the subject matter deemed acceptable for examination in the present application as a result of restriction. Claim 10 is amended to correct a minor editorial error. Claims 14-16 remain pending, but withdrawn, being directed to methods of use of the elected composition subject matter. Claims 14-16 are amended to keep their scope commensurate with the composition-claims being examined. Claims 9 and 13 are amended to delete improper multiple dependency; new claims 46-48 are added to maintain the so-deleted subject matter in the application.

Restriction Requirement

Claims 1, 2, 8, 12, 15 and 17-45 are canceled pursuant to the standing Restriction Requirement. Applicants take due note of the Examiner's decision that each group of claims is a separately patentable invention one over the other, e.g. that kits of the invention are non-obvious, distinct subject matter over methods of the invention. Applicants further take due note of the decision by the Examiner that compositions representing portions of the elected composition (nucleic acid), antisense versions of the elected composition (nucleic acid) and ribozymes incorporating the elected composition (nucleic acids) and/or double-stranded nucleic acids of the invention are deemed separately patentable and non-obvious subject matter over the elected compositions of the invention.

The number of species recited in the present claims 3-7, 9-11 and 13 has been limited as requested by the Examiner pursuant to the standing Restriction Requirement.

Claims 14-16, representing groups IV-VI, respectively, are maintained. These claims are directed to methods of use of the composition of the elected group, and so Applicants submit that, upon finding of allowable subject matter in the compositions of Group II, the corresponding method claims 14-16, if commensurate in scope with the allowable claims of Group II, should be rejoined to the present application and also allowed. MPEP 821.04.

Objections to the specification

The Examiner objects to the specification because of incorporation of browser executable hyperlinks. This subject matter is deleted from the specification and the references are replaced with generic description of the websites cited.

Utility

Claims 3-7, 9-11 and 13 stand rejected under 35 U.S.C. § 101 because the specification allegedly fails to disclose a substantial and specific utility for the presently claimed invention and such is also not readily apparent from the nature of the invention. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicants submit that the Examiner's assertion is based upon a mischaracterization of the disclosure. In particular, Applicants note that the Examiner has plainly overlooked description in the application related to the biochemical activity of the protein encoded by the elected nucleic acid (SEQ ID NO: 87) comprising a polynucleotide having the sequence of SEQ ID NO: 88.

Example 2 of the present application, beginning on page 64 of the specification, describes that expression of a protein encoded by a nucleic acid of SEQ ID NO: 88 provides activation of NF-kB in a cell, confirming the biochemical activity of the protein encoded by SEQ ID NO: 88

in accord with the prediction made based upon sequence homology. Thus, all of the speculation of the Examiner regarding the predictability of utility based upon sequence homology is groundless. The present application includes evidence that directly refutes the Examiner's position.

Applicants further note the experimental data provided in the attached Exhibit 1, which present results of an experiment comparing the expression of a nucleic acid of the present invention with expression of nucleic acids asserted as novelty-destroying prior art by the Examiner. These data were collected using a "Reporter Assay System" similar to that described in Example 2, i.e. a luciferase gene operatively linked to a NF-kB dependent promoter, and show that expressing a nucleic acid of the present invention results in up-regulation of NF-kB activity in a cultured cell.

The Examiner also asserts that, even if the protein of SEQ ID NO: 87 (which is encoded by the nucleic acid of SEQ ID NO: 88) has the asserted activity, there is no nexus shown between any disease and the biochemical activity asserted for the encoded protein. The Examiner's position on this issue is also factually incorrect.

First, the present specification discloses the relationship between NF-kB and immune system activation and inflammation. See, e.g. page 40-41. Applicants would also point out the references cited in support of the assertions of the specification, copies of which are provided attached hereto for convenient review by the Examiner:

R1: Clinical Chemistry 45, 7-17 (1999)

R2: J Clin. Pharmacol. 38, 981-993 (1998)

R3: Gut 43, 856-860 (1998)

R4: The New England Journal of Medicine 366, 10664071 (1997)

R5: TiPS 46-50 (1997)

R6: The FASEB Journal 9, 899-909 (1995)

R7: Nature 395 225-226 (1998)

R8: Science 278, 818-819(1997)

R9: Cell 91, 299-302 (1997)

Furthermore, Applicants note the following specific disclosure in the references, which may be outlined as follows:

A: Activation of NF-kB is related to diseases

- A.0 Activation of NF-kB is related with diseases (general description).
- A.1 Factors related with diseases give rise to activation of NF-kB.
- A.2 Activated NF-kB increases the expression of genes for many pathogenesis-related proteins and disease-mediator proteins.
- A.3 NF-kB levels are increased in patients.
- A.4 Prevention of NF-kB in model animal results in amelioration of disease.

B: NF-kB is a target for developing pharmaceutical treatments for such diseases.

C: Factors related to activation of NF-kB are targets for developing pharmaceutical treatments of such diseases.

D: Activation of NF-kB can be measured by NF-kB reporter assay.

From reference R1

< content related to A.0 and B >

At page 12, left column, lines 4-9:

"The key role that NF-kB plays in controlling the expression of multiple inflammatory and immune genes involved in toxic shock, acute phase responses, radiation damage, asthma, rheumatoid arthritis, atherosclerosis, cancer and AIDS makes this factor a central and favorable target for therapeutic intervention of diseases (1-3)."

< content related to D>

At page 13, right column, lines 36-41:

"The functional characteristic of NF-kB can be determined experimentally by assaying the expressing kB-dependent reporter genes. Traditionally, a reporter construct containing

chloramphenicol acetyltransferase or luciferase reporter genes under the control of kB elements in transfected into cells."

From reference R2

< content related to A.0 and A.2 >

At page 986, left column, lines.44-49:

"For each of the mediators cited, NF-kB binding sites exist on the promoter or enhancer region of their encoding genes (Table I). Therefore, NF-kB-related immune and inflammatory processes are involved in the pathogenesis of allograft rejection."

< content related to A.0, A.2, and A.3 >

At page 986, right column, lines 29-33:

"Because NF-kB binding motifs are located in the promoters or enhancers of these enzymes, cytokines, and adhesion molecules (Table I), NF-kB activation is undoubtedly involved in the pathogenesis of RA [rheumatoid arthritis]."

At page 986, right column, lines 38-50:

"Handel et al reported marked expression of NF-kBl and RelA in synovial tissue from patients with RA, Sakurada et al observed NF-kB nuclear translocation during the cell surface expression of 'CAM-1 and in the production of IL-6, IL-8, and GM-CSF. Roshak et al demonstrated that the nuclear translocation of RelA and c-Rel induced by IL-1 treatment upregulated COX-2 and phospholipase A2 (PLA2) gene expression with subsequent prostaglandin E2 producton in human rheumatoid synovial fibroblasts."

< content related to A.0 and A.2 >

At page 987, left column, lines 14-16:

"NF-kB plays an important role in the amplification and perpetuation of the inflammatory process in asthma."

At page 987, left column, lines 22-27:

"Der p1, the major allergen from house dust mites, is known to induce the transcription of genes for GM-CSF and RANTES by promoting nuclear translocation of NF-kB through phosphorylation and degradation of IkB- a in asthmatic bronchial epithelial cells."

< content related to A.0, A.2, and A.3 >

At page 987, left column, lines 46-48:

"The pathogenesis of septic shock therefore involves NF-kB activation."

At page 987, left column, lines 38-44:

"The generation of these endogenous mediators in septic shock has been linked to NF-kB activation. Nuclear extracts from peripheral blood mononuclear cells from nonsurviving patients with septic shock demonstrate increased nuclear binding activity of NP-kB compared with survivors."

< content related to A.3 and A.4 >

At page 987, the bridging paragraph of left column and right column:

"Experimental colitis in mice has been effectively blocked by the administration of antisense oligonucleotides to the RelA subunit of NF-kB. NF-kB in alveolar macrophages from patients with adult respiratory distress syndrome was upregulated to a significantly higher degree than in other pulmonary diseases, such as chronic obstructive pulmonary disease. Increase NF-kB activation also correlated with increased local concentrations of TNF- *a*, IL-1, IL-6, and 1L-8 in alveolar macrophages from patients with adult respiratory distress syndrome. NF-kB activation has been observed at the A_Q-containing plaques of patients with Alzheimer disease."

From reference R3

< content related to A.3 >

At page 859, left column, lines 16-18:

"it was found that nudear NF-kB levels are increased in patients with IBD."

<content related to A4 >

At page 859, left column, lines 29-31:

"Furthermore, in a murine model of colitis p65 antisense treatment led to an abrogation of chronic intestinal inflammation."

< content related to B >

At page 859, bridging sentence of left column and right column: "Thus, the above data suggest that targeting of NF-kB may be a novel molecular approach for the treatment of patients with IBD that could lead to the design of new treatment strategies that have added specificity but reduced toxicity compared with standard immunosuppressive therapy."

From reference R4

< content related to A.2 >

At page 1067, left column, lines 33-35:

"NF'-kB increases the expression of the genes for many cytokines, enzymes, and adhesion molecules in chronic inflammatory diseases."

< content related to A.3 and C >

At page 1067, bridging sentence of left column and right column:

"The production of interleukin-1 *S* , TNF- *a* , interleukin-6, granulocyte-macrophage colony-stimulating factor, *and* many chemotactic cytokines (cheraokines) is increased in patients with asthma, rheumatoid arthritis, psoriasis, and inflammatory bowel disease."

At page 1067, from line 26 of left column through line 10 of right column:

"The proinflammatory cytokines interleukin-1 and TNF- *a* both activate and are activated by NF-kB. Interleukin-1 S and TNF- a may influence the severity of disease, possibly by the persistent activation of NF-kB. The treatment of patients with rheumatoid arthritis with antibodies to TNF- a can control refractory disease,"

<content related to B>

At page 1069, right column, lines 17-19:

"NF-kB is therefore an obvious target for new types of anti-inflammatory treatment."

From reference R5

< content related to A.1 >

At page 46, left column, lines 4-8:

"While the causes of athma remain obscure, there have been important advances in understanding the underlying inflammatory processes."

At page 46, middle column, lines 26-31:

"Although many transcription factors are involved in the regulation of these inflammatory genes, one, nuclear factor-kB (NF-kB), apears to be of particular importance."

At page 47, middle column, lines 11-13:

"Many of the stimuli that increase inflammation in asthmatic airways result in the activation of NF-kB."

< content related to A.2 >

At page 48, middle column, lines 2-5:

"Many of the inflammatory proteins that are expressed in asthmatic airways are regulated, at least in part, by NF-kB."

< content related to B >

At page 50, left column, lines 41-43:

"NF-kB is a compelling target for the development of new antiinflammatory drugs for asthma."

From reference R6

< content related to A.0 >

At page 899, left column, line 7 from the bottom to right column, line 17:

"The recruitment of leukocytes from the circulation into the extravascular space is critical for inflammatory responses and repair o f tissue injury. ...Expression of some of the endothelial-leukocyte adhesion molecules is dynamically regulated at sites of leukocyte recruitment. For example, endothelial expression of E-selectin and vascular cell adhesion molecule-1 (VCAM-1) is dramatically induced, and expression of intercellular adhesion molecule-1 (ICAM-1) is substantially increased at sites of inflammation."

At page 900, bridging sentence of left column and right column: "Evidence is accumulating that the transcription factor NF-kB and its inhibitors may play a key role in regulating vascular pathophysiology."

< content related to A.1 and A.2 >

At page 901, left column, lines 5-10:

"NF-kB can be activated by a variety of signals relevant to endothelial pathophysiology. This list of activating agents includes the inflammatory cytokines interleukin-1$ (IIr1$) and tumor necrosis factor- a (TNF a), lipopolysaccharide (LPS), the viral homolog, poly(I:C), as well as oxidative and fluid mechanical stress."

At page 901, left column, lines 30-33:

"Once translocated to the nucleus, p501p65 binds to the kB sites in a variety of genes, including elements in the E-selectin, VCAM-1, and ICAM-1 promoters."

From reference R7

< content related to A.0 >

At page 225, middle column, lines 10-6 from the bottom: "NF-kB is critical for proper immune function, cell growth and survival, and anomalous activation is associated with inflammatory and neoplastic diseases and viral infection."

From reference R8

< content related to A.0 >

At page 818, left column, lines 25-23 from the bottom:

"The transcriptional activator protein NF-kB mediates key immune and inflammatory responses."

From reference R9

< content related to A.0 >

At page 299, left column, first paragraph, lines 8-10:

"Since its initial description, our view of the role of NF-kB in immune and inflammatory responses has broadened significantly:"

< content related to A.1 >

At page 299, left column, second paragraph, lines 2-9:

"NF-kB is activated by a vast number of agents including cytokines like tumor necrosis factor a (TNF a) and interleukin-1 (IL-1), bacterial LPS, viral infection and expression of certain viral proteins like Tax of human T -cell leukemia virus, (HTLV 1), antigen receptor cross-linking of T and B cells, calcium ionophores, phorbol esters, UV radiation, free radicals, endoplasmic reticulum overloading, and others."

< content related to A.2 >

At page 299, left column, second paragraph, lines 11-16:

"The genes regulated by the NF-kB family of transcription factors are diverse and include those involved in immune function, inflammatory response, cell adhesion, and growth control. Recently, the activation of NF-kB has also been linked to the regulation of cell death."

From the above, it is plain that one of ordinary skill in the art, upon reading the present specification, would understand that the present invention has utility at least as a tool for screening for compounds that affect the NF-kB pathway in mammalian organisms and that

compounds effective in such a screen would have utility in treating diseases related to problems in that pathway such as immune system dysfunction and inflammation, as described in detail at pp. 40-41 of the specification. Accordingly, the instant rejection under 35 U.S.C. § 101, for alleged lack of utility of the invention, should be withdrawn.

Rejections over prior art

Claims 3-6 stand rejected under 35 U.S.C. § 102(e) as being anticipated by SEQ ID NO: 15 of US 200030012966. The Examiner asserts that this sequence has 99% sequence identity to SEQ ID NO: 88 of the present application and furthermore has significant continuous lengths of sequence that match the present sequence SEQ ID NO: 88 to provide for hybridization under stringent conditions.

Applicants attach hereto a Declaration of Shuji Muramatsu, which shows data from an experiment in which activation of NF-kB was assessed in the reporter gene assay system as used in Example 2 of the instant specification to determine if the proteins of SEQ ID NOS: 34 and 53, both described as encoded by SEQ ID NO: 15 of US 200030012966, were functional. The expressed proteins were also examined by Western blotting using an antibody directed against GFP.

As can be seen in Figures C and D of the Muramatsu Declaration, the proteins encoded by SEQ ID NO: 15 are both of a size distinct from that of the protein of SEQ ID NO: 87, which is encoded by the presently claim nucleic acid, and furthermore, the proteins of the cited reference do not exhibit any activity of activating NF-kB. These proteins are therefore different from the proteins encoded by the present SEQ ID NO:88.

Thus, the polyucleotide of SEQ ID NO: 15 of US 200030012966 does not anticipate the presently claimed invention and the instant rejection should be withdrawn.

In view of the above amendment, Applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell (Reg. No. 36,623) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Dated: June 30, 2006

Respectfully submitted,

By _____

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Attachments: Declaration Under 37 C.F.R. § 1.132 with Figures A-D (9 pages)